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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/880,988	Applicant(s) CANTOR ET AL.	
	Examiner Arun Chakrabarti	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-20 and 25-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-20 and 25-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Election/Restriction

1. Applicant's election, without traverse of Group I, corresponding to claims 1-8, 10-20, and 25-45, in Paper NO: 9 is hereby acknowledged.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 4 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 8 are rejected over the use of improper Markush language. The phrase, "selected from the group consisting of" is suggested.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3, 5-7, 10-12, and 25-27 are rejected under 35 U.S.C. 102 (b) as being anticipated by Brennan (U.S. Patent 5,174,962) (December 29, 1992).

Brennan teaches a method for identifying nucleotides at one or more base positions and determining the nucleotide sequence of a plurality of target nucleic acid molecules (Abstract, and Column 6, lines 12-23), comprising:

a) synthesizing extension products of the target nucleic acid in the presence of chain terminating nucleotides and mass-matched nucleotides (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4, and Schemes D and E);

b) determining the mass of each extension product (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4);

c) calculating a mass shift from a period for the mass of each extension product (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4, and Figure 2B),

whereby nucleotides at one or more base positions and the sequence is determined by identifying the nucleotide that corresponds to each mass shift (Column 6, lines 10-64).

Brennan teaches a method, wherein the mass-matched deoxynucleotides are identical (Figures 1 and 2B).

Brennan also teaches a method for determining the nucleotide sequence of a plurality of target nucleic acid molecules by incorporating pair-matched nucleotides into the target nucleic acid (Abstract, and Column 6, line 65 to column 10, line 64).

Brennan also teaches a method, wherein the chain-terminating nucleotide base pairs are mass-matched and have distinct molecular weights (Scheme E, and Column 10, lines 47-64).

Brennan inherently teaches a method for detecting different nucleotide base compositions in a population of nucleic acids having identical length and different base compositions with respect to the difference of a single base (Column 11, lines 1-38, in this case DNA sequence of any genetic material and Figures 1-2) comprising:

a) synthesizing the nucleic acids in the presence of one or more nucleotide analogs to produce synthesized nucleic acids (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4, and Schemes D and E); and

b) determining a mass of each synthesized nucleic acid (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4);

whereby different nucleotide base compositions are detected by determining the mass of each synthesized nucleic acid (Column 5, line 25 to column 6, line 8, and Examples 1-4, and Figure 2B),

wherein the nucleotide analog separates the masses of nucleic acids having different base compositions in a predetermined interval (Figures 1-2).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-8,10-12, and 25-27 are rejected under 35 U.S.C. 103 (a) over Brennan (U.S. Patent 5,174,962) (December 29, 1992) in view of Schulz (U.S. Patent 6,232,076 B1) (May 15, 2001).

Brennan teaches a method of claims 1-3, 5-7, 10-12, and 25-27 as described above.

Brennan does not teach a method, wherein the mass-matched deoxynucleotide is deoxyinosine.

Schulz teaches a method, wherein the mass-matched deoxynucleotide is deoxyinosine (Column 8, lines 16-36).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine, within the method of Brennan, the method wherein the mass-matched deoxynucleotide is deoxyinosine of Schulz since Schulz states, "The

polymerase extension product can also include other nucleotides which may be useful replacements for any of the above (deoxyadenosine, deoxyguanosine, deoxycytidine, deoxythymidine, etc) . Non limiting examples are deoxyinosine monophosphates (Column 8, lines 25-36)". An ordinary artisan would have been motivated by the express statement of Schulz to substitute and combine, within the method of Brennan, the method wherein the mass-matched deoxynucleotide is deoxyinosine of Schulz in order to achieve the express advantages, as noted by Schulz, of a nucleotide system which may be useful replacements for any of the deoxyadenosine, deoxyguanosine, deoxycytidine, deoxythymidine, etc.

8. Claims 1-3, 5-7, 10-12, and 25-45 are rejected under 35 U.S.C. 103 (a) over Brennan (U.S. Patent 5,174,962) (December 29, 1992) in view of Shuber (U.S. Patent 5,888,778) (March 30, 1999).

Brennan teaches a method of claims 1-3, 5-7, 10-12, and 25-27 as described above including determining the mass of the extended nucleic acids by mass spectrometry.

Brennan does not teach a method for detecting a mutation in a target nucleic acid sequence in a target nucleic acid molecule, in a sample, comprising:

a) hybridizing a nucleic acid molecule a primer to nucleic acid molecule in the sample, thereby producing a hybridized primer and a molecule from the sample;

wherein the primer is complementary to a sequence in the target nucleic acid that is adjacent to the region suspected of containing a mutation sequence;

b) contacting the hybridized primer with a composition comprising mass-matched deoxyribonucleoside triphosphates and a chain terminating nucleotide selected from a dideoxyribonucleoside triphosphate, such that the hybridized primer is extended until a chain terminating nucleotide is incorporated, thereby producing an extended primer ; and

c) determining the mass of the extended primer by mass spectrometry, thereby determining whether a mutation is present in the target nucleic acid sequence.

Shuber teaches a method for detecting a mutation in a target nucleic acid sequence in a target nucleic acid molecule, in a sample (Abstract), comprising:

a) hybridizing a single or plurality of primers to nucleic acid molecule in the sample, thereby producing a hybridized primer and a molecule from the sample (Column 7, lines 38-42);

wherein the primers are complementary to a sequence in the target nucleic acid that is adjacent to the region suspected of containing a mutation sequence (Column 7, lines 38-59, and Claims 1, 10, and 13);

b) contacting the hybridized primer with a composition comprising mass-matched deoxyribonucleoside triphosphates and a chain terminating nucleotide selected from a dideoxyribonucleoside triphosphate, such that the hybridized primer is extended until a chain terminating nucleotide is incorporated, thereby producing an extended primer (Column 7, lines 38-59, and Claims 1, 10, and 13);

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine, within the mass spectrometric method of

Brennan, the method of single and multiple primers designed to detect mutation of Shuber since Shuber states, "Moreover, due to their increased selectivity for target, methods of the invention may be used to detect and identify a target nucleic acid that is available in small proportion in a sample, and that would normally have to be amplified by, for example, PCR in order to be detected (Column 7, lines 56-59)". An ordinary artisan would have been motivated by the express statement of Shuber to substitute and combine, within the mass spectrometric method of Brennan, the method of single and multiple primers designed to detect mutation of Shuber in order to achieve the express advantages, as noted by Shuber, of an invention which due to their increased selectivity for target may be used to detect and identify a target nucleic acid that is available in small proportion in a sample, and that would normally have to be amplified by, for example, PCR in order to be detected.

9. Claims 1-3, 5-7, 10-20, and 25-27 are rejected under 35 U.S.C. 103 (a) over Brennan (U.S. Patent 5,174,962) (December 29, 1992) in view of Canard et al. (U.S. Patent 5,798,210) (August 25, 1998).

Brennan teaches a method of claims 1-3, 5-7, 10-12, and 25-27 as described above.

Brennan does not teach a method, wherein the primers are plurality of duplex hairpin primers ligated to the single-stranded templates.

Canard et al. teach a method, wherein the primers are plurality of duplex hairpin primers ligated to the single-stranded templates. (Column 21, line 12 to column 22, line 67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine, within the method of Brennan, the method wherein the primers are plurality of duplex hairpin primers ligated to the single-stranded templates of Canard et al. since Canard et al. state, "The use of hairpin primer makes it possible to use basic conditions for deprotection of the 3' hydroxyl compatible with a repetition of the procedure without addition of a primer at each step of the indirect determination of a nucleotide inserted. In fact, the rehybridization of the primer occurs intramolecularly and immediately (Column 4, line 66 to column 5, line 4)". An ordinary artisan would have been motivated by the express statement of Canard et al. to substitute and combine, within the method of Brennan, the method wherein the primers are plurality of duplex hairpin primers ligated to the single-stranded templates of Canard et al. in order to achieve the express advantages, as noted by Canard et al., of the use of hairpin primer, which makes it possible to use basic conditions for deprotection of the 3' hydroxyl compatible with a repetition of the procedure without addition of a primer at each step of the indirect determination of a nucleotide inserted and where the rehybridization of the primer occurs intramolecularly and immediately.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Arun Kr. Chakrabarti

ARUN K. CHAKRABARTI
PATENT EXAMINER

Arun Chakrabarti,

Patent Examiner,

March 18, 2002